PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2M/2BH90/SK/1	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/010879	International filing date *(day/month/year)* 27.09.2004	Priority date *(day/month/year)* 09.10.2003
International Patent Classification (IPC) or national classification and IPC G01N33/68, G01N33/94		
Applicant UNIVERSITEIT MAASTRICHT et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.05.2005	20.09.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Bigot-Maucher, C Telephone No. +49 89 2399-7415

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/010879

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-37	as originally filed
Claims, Numbers	
1-6	received on 11.07.2005 with letter of 08.07.2005
Drawings, Sheets	
1/17-17/17	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-6 (partially)

because:

☒ the said international application, or the said claims Nos. 1-4 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-6 (partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-6
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-6
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	5-6
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Item III:

1. Present claims 1-6 relate to an extremely large number of possible compounds/products/methods due to the broad term "non-myocytical marker". Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/products/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope was impossible. Consequently, the search has been carried out for those parts of claims 1-6 which appear to be supported and disclosed, namely those parts relating to the compounds/products/methods relating to thrombospondin-2 and galectin-3 (see p 5, para 1 to p 6, para 1; examples).

2. Claim 1, step (a) ("obtaining a biological sample"), dependent claims 2-3 and independent claim 4 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Item V:

1. Articles 33(2) and (3) PCT

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: Circulation,
vol 100, no 18 suppl., 1999, p 56 I

D2: Circulation,
vol 104, 2001, pp 2641-2644

D3: Journal of Investigative Dermatology,
vol 117, no 2, 2001, p 391

D4: Clin Exp Immunol, vol 124, 2001, pp 266-273
D5: J Clin Immunol, vol 15, no 6, 1995, pp 329-337

1.1. The subject-matter of **independent claim 1 is novel** (Article 33(2) PCT) in view of the prior art for the following reasons:

D1 discloses the involvement of thrombospondin-2 in myocardial infarction by examining mice lacking thrombospondin-2 (abstr).
D1 does not disclose any method for identifying a subject at risk of developing hypertensive end organ damage. The level of thrombospondin is not compared to a standard level. Myocardial infarction is neither a hypertensive end organ damage, nor a congestive heart failure.

D2 describes a protective effect of a variant of thrombospondin-2 against familial premature myocardial infarction (abstr).
ELISA is performed for thrombospondin-1 instead of thrombospondin-2 (p 2642, col 1, para 4).
D2 relates to familial premature myocardial infarction, which is a different disorder as compared to end organ failure such as congestive heart disease. Moreover, D2 relates to the correlation of genetic variations or mutations in an allele encoding thrombospondin-2. According to D2, not the level of thrombospondin-2 is indicative, but the presence of genetic variations in thrombospondin-2. No comparison with standard levels is performed.

D3 shows a detection of the level of thrombospondin-2 via ELISA. Thrombospondin-2 is shown as angiogenesis inhibitor (abstr).
Heart diseases are not mentioned, methods for identifying a subject at risk of developing hypertensive end organ damage even less.

D4 reveals the determination of serum levels of Galectin-1 in cardiac Chagas' disease by ELISA (p 267, col 2, para 4; abstr).
Galectin-3 is not mentioned.

In D5 the determination of the level of Galectin-3 in autoimmune disease using an ELISA is described (abstr).
No heart disease is mentioned.

Thus, none of the documents, either taken alone or in any combination, discloses a method for identifying a subject at risk of developing hypertensive end organ damage, and even less by using galectin-3 or thrombospondin-2 as marker therefor.

Therefore, **claim 1 is considered inventive** (Article 33(3) PCT).

The same applies to dependent claims 2-3.

1.2. The subject-matter of **independent claim 4 is novel and inventive** for similar reasons as independent claim 1: none of the prior art documents reveals that galectin-3 or thrombospondin-2 is involved in hypertensive end organ damage.

1.3. The subject-matter of **independent claim 5 is novel and inventive** for similar reasons as independent claim 1: none of the documents discloses congestive heart failure or hypertensive end organ damage, and even less involvement of galectin-3 therein.

1.4. The subject-matter of **independent claim 6 is novel and inventive** for similar reasons as independent claim 1: none of the documents discloses the involvement of thrombospondin-2 in congestive heart failure or hypertensive end organ damage.

2. Industrial applicability

The subject-matter of claims 5-6 is industrial applicable (Article 34(4)(a)(i) PCT).

International application PCT/ EP2004/010879
enclosure to letter dated 08-07-2005

CLAIMS

1. Method for identifying a subject at risk of hypertensive end organ damage, comprising:

(a) obtaining a biological sample of said subject;

(b) determining the level of at least one non-myocytical marker in said sample, wherein the non-myocytal marker is selected from the group consisting of galectin-3 and thrombospondin-2;

(c) comparing the level of said marker to a standard level; and

(d) determining whether the level of the marker is indicative of a risk for developing hypertensive end organ damage.

2. Method as claimed in claim 1, wherein the biological sample is a plasma sample derived from peripheral blood.

3. Method as claimed in claim 1 or 2, wherein the level of the marker is measured by an enzyme-linked immunosorbent assay (ELISA).

4. Use of one or more non-myocytal markers for identifying a subject at risk of developing hypertensive end organ damage, wherein the non-myocytal marker is selected from the group consisting of galectin-3 and thrombospondin-2.

5. Use of galectin-3 for the manufacture of a medicament for the prevention and/or treatment of congestive heart failure and/or hypertensive end organ damage.

6. Use of thrombospondin-2 for the manufacture of a medicament for the prevention and/or treatment of congestive heart failure and/or hypertensive end organ damage.